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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,731	07/27/2000	Man Sung Co	GNN-5315DV2	5819

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Finnegan Henderson Farabow Garrett & Dunner LLP
1300 I Street N W
Washington, DC 20005-3315

EXAMINER

GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 09/09/2003

29

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/626731

Applicant(s)

CO ETAL.

Examiner

GAMBEL

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 6/26/03
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 6/26/03 (Paper No. 22) has been entered.

Applicant's amendment, filed 6/26/03 (Paper No. 23), has been entered.

Claims 1 and 9 have been amended.

Claim 11 has been added.

Claims 1-11 are under consideration in the instant application.

2. This Office Action will be in response to applicant's arguments, filed 6/26/03 (Paper No. 22).

The rejections of record can be found in the previous Office Actions (Paper Nos. 10/15/18).

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-10 and newly added claim 11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Blazar et al. (WO 95/34320) (1449) (see entire document) essentially for the reasons of record.

Applicant's amended claims and arguments, filed 6/26/03 (Paper No. 22), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper Nos. 10/15/18.

Applicant essentially argues that Blazar et al. do not teach contacting the donor cells with B7-1-specific / B7-2-specific antibodies and recipient cells from the patient for a period of time of "from about 1 to about 48 hours before being introduced into the patient".

Applicant acknowledges that Blazar et al. Teach saturating B7 with inhibitors such as hCTLA-4Ig and anti-LFA-1 for 3 hours.

However, applicant asserts that the claims are not drawn to "inhibitors" but rather drawn to "contacting the donor cells with an immunoglobulin specific to B7-1 and an immunoglobulin specific for B7-2 ... from about 1 to 48 hours".

It is acknowledged that the Blazar's Examples of CTLA-4Ig is not an immunoglobulin and that anti-LFA-1 antibodies do not recognize B7-1 nor B7-2.

In addition, applicant asserts that Blazar teaches a priming step of contacting donor and recipient cells for 2.5-4 days before the mixture is contacted with CTLA-4Ig and anti-LFA-1, which is distinguishable from the claimed limitation of "contact for a period of time from about 1 to 48 hours".

Although applicant points to the teaching of incubating donor and recipient cells with antibodies for about 2.5 to 4 days by Blazar et al., Blazar et al. teach saturating B7 with inhibitors such as hCTLA-4Ig and anti-LFA-1 for 3 hours (see pages 28-29, overlapping paragraph). Therefore, Blazar et al. does teach saturating B7 with inhibitors with the newly added claimed limitations (e.g. 3 hours).

It is noted that the claimed methods recite "comprising" which does not exclude additional, unrecited elements or method steps. See MPEP 2111.03.

Again, Blazar et al. teach the use of inhibitors including those that bind both B7-1 and B7-2 (e.g. Summary of the Invention, including page 4, paragraph 1; Detailed Description of the Invention, including page 6 - page 7, paragraph 1, page 17, paragraph 1 and Uses of the Invention, page 11, paragraph) to induce T cell unresponsiveness for bone marrow transplantation, including its use for the treatment of hematological malignancies and anemia (e.g. see Background of the Invention, Summary of the Invention and Uses of the Invention).

In addition, Blazar et al. teach the inhibitory agents can be administered for 18-36 hours after T cell priming e.g. see page 23, paragraph 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. Bone marrow comprise lymphocytes, stem cells and immature blood cells. The claimed functional limitations and constructions encompassed by the claims would be inherent properties of the referenced methods to induce T cell responsiveness with B7-1 and B7-2-specific antibodies for bone marrow transplantation in the treatment of malignancies and anemia.

Further, it is noted that Blazar teaches recombinant, including humanized antibodies (see Antibodies on pages 9-15, particularly pages 13-15).

Applicant's arguments are not found persuasive.

6. Claims 1-10 and newly added claim 11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320) (1449) alone or in combination with Chappel et al. (U.S. Patent No. 6,096,537), Dinsmore et al. (U.S. Patent No. 5,919,449) and Goldberg et al. (Transplant Immunology 2: 27-34, 1994) essentially for the reasons of record.

Dinsmore et al. has been added herein to support the position that the prior art provides sufficient motivation and expectation of success for providing an inhibitory antibody to meet the individual need and professional of the judgment of the person administering or supervising the administration of the compositions to achieve the desired immunosuppressive effects, including prior treatment for one to three days (e.g. see entire document, including columns 15-17) and exemplifies modifying cells to be transplanted with an antibody for one hour (see Example III, on column 20).

Goldberg et al. teach the pretreatment of renal transplants with inhibitory antibodies to prolong allograft survival and teach the ex vivo pretreatment of said inhibitory antibodies can occur from 20 minutes to 14 hours and employed 1 hour for subsequent studies (See entire document, including page 31, Determination of optimal concentration of perfused antibody).

Therefore, Dinsmore et al. and Goldberg et al. provide further evidence that the ordinary artisan modified transplants ex vivo with inhibitory antibodies for various times, including those times encompassed by the claimed invention, to achieve the immunosuppression of deleterious immune responses to the grafted cells, tissues and organs.

Applicant's amended claims and arguments, filed 6/26/03 (Paper No. 22), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper Nos. 15/18 and reiterated herein for applicant's convenience.

Again, applicant argues that Blazar uses the 3 hour incubation period after a priming step of 2.5-4 days (see Blazar, page 28, line 33-page 29, line 12) and asserts that a priming step is not recited in the claims.

Again, applicant argues that Blazar teaches away from performing an in vitro incubation step targeting only one pathway.

It is noted that the claimed methods recite "comprising" which does not exclude additional, unrecited elements or method steps. See MPEP 2111.03

Again, applicant argues that Chappel does not teach nor suggest the ex vivo application of antibodies to B7-1 or B7-2 in a method of transplanting cells. Therefore, applicant asserts that Chappel merely suggest the use of a 30 minute in vitro incubation step with reagents that target molecules distinct from the claimed invention.

In teaching combined in vitro and in vivo treatment regimens, Blazar et al. teach the agents serve to inhibit T cell proliferation, T cell signaling T cell costimulation or T cell adhesion (e.g. see page 22, paragraph 2).

In teaching the use of suitable agents or antibodies, Chappel teach that the antibody pretreatment serves to inhibit or prevent rejection of the transplanted cells or tissues.

As indicated previously and above, Blazar et al. teach the use of inhibitors including those that bind both B7-1 and B7-2 (e.g. Summary of the Invention, including page 4, paragraph 1; Detailed Description of the Invention, including page 6 - page 7, paragraph 1, page 17, paragraph 1 and Uses of the Invention, page 11, paragraph) to induce T cell unresponsiveness for bone marrow transplantation, including its use for the treatment of hematological malignancies and anemia (e.g. see Background of the Invention, Summary of the Invention and Uses of the Invention). In addition, Blazar et al. teach the inhibitory agents can be administered for 18-36 hours after T cell priming e.g. see page 23, paragraph 1). Bone marrow comprise lymphocytes, stem cells and immature blood cells. The claimed functional limitations and constructions encompassed by the claims would be intrinsic properties of the referenced methods to induce T cell responsiveness with B7-1 and B7-2-specific antibodies for bone marrow transplantation in the treatment of malignancies and anemia.

Although applicant points to page 28, lines 20-32 for the teaching of incubating donor and recipient cells with antibodies for about 2.5 to 4 days by Blazar et al., Blazar et al. teach saturating B7 with inhibitors such as hCTLA-4-Ig and anti-LFA-1 for 3 hours (see pages 28-29, overlapping paragraph and Experiment 3 on page 31). Therefore, Blazar et al. does teach saturating B7 with inhibitors with the newly added claimed limitations (e.g. 3 hours).

Blazar et al. differs from the claimed methods by not disclosing the range of about 1- 24 hours per se. Given the teaching of Blazar et al., including saturating B7 with inhibitors such as hCTLA-4-Ig and anti-LFA-1 for 3 hours (see pages 28-29, overlapping paragraph and Experiment 3 on page 31). It is noted that Experiment 3 on page 31 discloses that the inclusion of the priming step in the treatment regiment can increase the inhibitory effects of the agents.

Given the teaching of Blazar et al. that the in vitro incubation step with agents that block B7 factors the development of donor anti-host specific hyporesponsiveness (In vitro incubation of splenocytes with agents on pages 28-29) with the example of 3 hours (pages 28-29 and 31), one of ordinary skill in the art would be motivated to select those times of incubating donor cells with B7-specific inhibitors to achieve donor anti-host specific hyporesponsiveness, consistent with the claimed therapeutic endpoints. One of ordinary skill in the art would have appreciated that various times including times of about 1 -24 hours would have been suitable depending on the nature of the donor cells and the nature of the agents and conditions suitable to achieve donor anti-host specific hyporesponsiveness.

In addition, it is noted that Chappel et al. teach masking antigens to achieve or to induce immunological nonresponsiveness can be for 30 minutes (see entire document, including column 8, paragraph 1 and column 18, paragraph 1), which reads on "about 1 hour" of the claimed methods. It is noted that Chappel et al. exemplify masking murine pancreatic islet cells and not the mixture of cells taught by Blazar et al. or that encompassed by the claimed methods.

As pointed out above, Dinsmore et al. and Goldberg et al. provide further evidence (e.g. one hour, 20 minutes to 14 hours) that the ordinary artisan modified transplants ex vivo with inhibitory antibodies for various times, including those times encompassed by the claimed invention, to achieve the immunosuppression of deleterious immune responses to the grafted cells, tissues and organs

Given the prior art teachings of Blazar et al., Chappel et al., Dinsmore et al. And Goldberg et al., one of ordinary skill would have been motivated to pretreat donor cells for a period of time to achieve or to induce donor anti-host specific hyporesponsiveness. Given such teachings, one of ordinary skill in the art would have expected that a range of times, including that encompassed by the claimed "about 1-24 hours" would have been met at the time the invention was made given the nature of the donor cells, and to achieve the desired immunosuppressive goal to prolong transplant survival.

Given the teachings of the prior art references, including the Examples described by Blazar et al., Chappel et al, Dinsmore et al. and Goldberg et al.; one of ordinary skill in the art would have appreciated that achieving immunological nonresponsiveness by pretreating donor cells with B7-specific inhibitors would have varied depending on the nature of the donor cells, the nature of the agents and the conditions suitable for achieving said immunological nonresponsiveness.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention, including a range of "about 1 - 24 hours" or pretreating donor cells with B7-specific inhibitors to achieve immunological nonresponsiveness. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.



Phillip Gambel, Ph.D.
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Technology Center 1600
September 8, 2003